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Bacteria enhance tumorigenesis through activating intestinal stem cells related signaling pathways

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The number of microbial cells is about 10 times larger than the number of eukaryotic cells in the human body. Enteric bacteria play an important role in the pathogenesis of cancer. Due to the complexity of the gut flora, identification of the specific microbial agents contributing to colon cancer remains challenging. How bacterial products directly contribute to cancer is still unknown. Bacteria can modulate the host by secreting bacterial effector proteins to the host cells. *AvrA* is a pathogenic protein of enteric bacteria that influences eukaryotic cell pathways utilizing ubiquitin and acetylation. We hypothesize that the bacterial effector AvrA activates the STAT/beta-catenin pathway to promote colonic tumorigenesis. We investigated a chronic bacterial infected cancer model with *Salmonella* colonization in the mouse intestine. Mice were colonized with AvrA- sufficient or deficient bacterial strains, then stimulated with a carcinogen azoxymethane and dextran sodium sulfate (induced colitis). We found that mice infected with AvrA-expressed bacteria had significantly high incidence of tumor in colon. AvrA expression decreased the phosphorylated-beta-catenin and inhibits the ubiquitination of beta-catenin in mouse colonic epithelial cells *in vivo*. Additionally, AvrA expression enhanced the acetylated beta-catenin, which regulates the beta-catenin transcription activity. Moreover, infected colon had higher STAT 1 and 3 expressions. Inflammatory cytokines such as IL-6 and INF-gamma in serum were increased. Overall, AvrA activation of the STAT/beta-catenin pathway promoted colonic tumorigenesis. The current study provides important insights into intestinal infection and cancer stem cells. Our findings can also be applied to the risk assessment and prevention of cancer.

Biography

Dr. Jun Sun is currently an Assistant Professor at the University of Rochester. Her key achievements include identification and characterization of bacterial effector protein AvrA that activates the Wnt/beta-catenin pathway and affects intestinal epithelial stem cells in inflammation. Her long-range goal is to elucidate how a specific bacterial effector provides a mechanistic link between inflammation of the intestine and the development of colon cancer. Dr. Sun is the author of 58 peer-reviewed papers, numerous chapters and invited reviews. She is an inventor of two patents. Her current researches are supported by the NIH, NY STEM, and the American Cancer Society.